Cholinesterase inhibitors for Alzheimer's disease and the heart: an update.

Mini review

Jos Tournoy[1], Lorenz Van der Linden[2]

1. Memory Clinic and Geriatric Medicine, University Hospitals Leuven & Department of Clinical and Experimental Medicine, KU Leuven, Belgium
2. Pharmacy Department, University Hospitals Leuven & Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium

Abstract Acetylcholinesterase inhibitors (AChEIs) are widely used in the symptomatic treatment of Alzheimer's disease, a disease that is afflicting a major part of our greying population. Their mechanism of action is based upon non-specific cholinergic stimulation, thereby potentially inducing cardiac beneficial or adverse effects. Data of large observational studies demonstrated a small but significant cardiac risk for all registered AChEIs (donepezil, galantamine and rivastigmine) not observed in previous clinical trials. This might be explained by a non-selective approach for prescribing AChEIs, thereby also including older persons with coexisting diseases or using several drugs, opposed to a selective patient recruitment in trials. Although there is no consensus on the management, we recommend attentiveness for cardiac symptoms and heart rhythm in every patient treated with AChEIs, and plea for a vigilant use of AChEIs in elderly patients at increased risk for cardiac adverse effects.

Keywords Alzheimer's disease, cholinesterase inhibitors, cardiac effects

Introduction

For more than a decade now, acetylcholinesterase inhibitors (AchEIs) are recommended as a first line strategy in the symptomatic treatment of Alzheimer's disease (AD) and related disorders. Their mechanism of action is based upon the cholinergic hypothesis, alleviating symptoms by increasing cholinergic neurotransmission within the brain. Because of their nonspecific action mechanism, parasympathic side-effects can occur, and can be of clinical significance, especially in an older population suffering multiple comorbidities and prone to polypharmacy.

Cholinergic transmission in normal cognition and Alzheimer's disease

Cholinergic activity is recognized to be widespread in brain areas such as the hippocampus, septum, amygdala and neocortex, and crucial for higher cognitive functioning. When inhibiting cholinergic transmission by administering scopolamine, cognitive impairment resembling deficits as seen in AD occurs [1]. Postmortem brain autopsies of AD patients revealed a drastic reduction of cholinergic neurons as well as a reduced acetylcholinesterase activity in early affected areas such as the hippocampus. These findings led to the cholinergic hypothesis of Alzheimer's disease [2], which opened the road for the first approved drug therapies based on inhibiting this cholinesterase activity in the brain, thereby stimulating cholinergic transmission. Development of several compounds including tacrine, heptylphysostigmine and metrifonate was initiated but their tolerability limited broad clinical use [3]. At the end of the last century, the cholinesterase inhibitors donepezil, galantamine and rivastigmine were approved for market authorization for medical treatment for AD and are now widely available.

Mechanism of cholinergic transmission

Acetylcholine (ACh) is synthesized as a neurotransmitter from choline and acetyl-co-enzyme A, and subsequently stored in and released

from synaptic vesicles. It then binds to both pre- and postsynaptic nicotinic and muscarinic receptors. Nicotinic receptors are pentameric excitatory receptors localized in the central nervous system, autonomic ganglia, neuromuscular junctions and extramedullar glands of which 17 different subtypes exist [4, 5]. Muscarinic receptors are G-protein associated receptors in 5 subtypes: M1 in the central nervous system (CNS), autonomic ganglia and glandular tissue, M2 in the heart, M3 in smooth muscle and M4, 5 in the CNS [4]. Degradation of ACh is executed by two different cholinesterases; acetyl (AChE)- and butyrycholinestarase (BuChE). Where initially a predominant role was contributed to AChE, it now appears that both likely play a role in central cholinergic transmission [6]. AChE exists in three different isoforms, G1 (monomeric), G2 (dimeric) and G4 (tetrameric), all occurring in different brain areas but with a predominance of the G4 form. Isoforms G2 and G4 are also found outside of the CNS [7, 8].

Cognitive and functional effect of AChEIs in AD

AChEI have been approved for the treatment of mild to moderate forms of AD based on the results of several trials with the available drugs. They act symptomatically without changing the course of the disease. They slow down deterioration of cognitive and functional decline and can positively affect behavioral disorders. Several national and international treatment guidelines recommend their use as a first line therapy for AD and a Cochrane review [9] confirmed their clinical effectiveness compared to placebo although effect sizes are moderate. As to now, no data support significant differences in effectiveness between donepezil, galantamine and rivastigmine.

Safety and tolerability of AChEIs

In the reported studies, most frequent side effects are related to gastrointestinal symptoms, such as nausea and vomiting. After a few days tolerance often occurs allowing therapy continuation. Several other more infrequent side effects have been reported as a result from central cholinergic activity including dizziness, convulsions, agitation, extrapyramidal symptoms and sleeping disorders. On the other hand, peripheral cholinergic side effects can manifest through diarrhea, rhinorrhea, muscle cramps, urinary incontinence or cardiorespiratory symptoms. The cardiac effects of AChEI therapy will be the further focus of this review.

Donepezil, galantamine and rivastigmine show distinct pharmacokinetics

Pharmacological profiles of registered AChEIs differ, leading to potential differential effects on cardiac functioning.

Donepezil

Donepezil is a quickly reversible AChEI with greater affinity for AChE than for BuChE. Specificity for the cerebral G1 isoform of AChE is relatively low, potentially stimulating peripheral cholinergic action, including cardio-inhibitory effects [8]. Donepezil is more than 90 %, protein bound , and has a half-life of about 3 days. It is metabolized by cytochrome P450 (CYP450) 2D6 and 3A4 and by glucuronidation, making it moderately prone to interaction with other drugs [8, 10].

Galantamine

Galantamine is a quickly reversible AChEI as well, also with greater affinity for AChE than for BuChE, but with a low specificity for the G1 isoform, potentially contributing to unwanted peripheral side effects [8]. Galantamine binds also to the postsynaptic nicotinic receptor thereby stimulating cholinergic transmission, but it is not known how clinically relevant this stimulation is. Plasma protein binding is low (18%) and half-life is 4-6h. It is partially metabolized by CYP2D6 and CYP3A4. No single pathway seems to be predominant [8, 10].

Rivastigmine

In contrast to the other registered AChEIs, rivastigmine is a slowly reversible AChEI with a similar affinity for AChE and BuChE. Rivastigmine has a higher specificity for isoform G1 present in brain, thus with a theoretical lower risk of cardio-inhibitory effects [8], although it is not known whether this is of any clinical significance. Half-life of rivastigmine is short (1-2 hours) and it is 40% protein bound. Rivastigmine has a favorable

interaction profile since the hepatic CYP450 isoenzymes are only minimally involved [8, 10].

Clinical relevance of cardiac events associated with AChEI use

Data related to clinical events differ in the initial prospective studies investigating safety and tolerability and effectiveness compared to the later published cases and cohort studies in the general population. Several reasons explain these discrepancies which will further be clarified.

Findings from trials towards safety, tolerability and effectiveness

All three marketed AChEIs investigated cardiac safety and tolerability for their use in AD patients. Several studies on their safety, including cardiac safety, were published, and we will refer to one study for each AChEI. In general, a non-significant reduction in heart rate of 2 to 3 beats per minute (bpm) was observed [11]. A double blind placebo controlled prospective study with donepezil (n=290) did not show any significant ECG changes [12] and incident bradycardia (HR≤ 60) was 10% compared to 7% in the placebo group. One death was reported and was unlikely related to treatment with donepezil. A double blind placebo controlled trial of galantamine in patients with AD did not demonstrate any significant effects on heart rate or ECG changes [13]. Incident mortality was 1,1% in the placebo arm versus 1,4% in the galantamine arm. Rivastigmine appeared safe and did not show any significant effect on heart rate, ECG changes or mortality in 697 AD patients [14]. In a larger meta-analysis including 4 double blind placebo controlled trials on 2756 patients with AD, rivastigmine did not demonstrate any significant changes of heart rate, PR or QTc interval [15]. These results suggest a very favorable clinical tolerance profile of all three AChEIs. A subsequently published subanalysis of the Cochrane review [9] demonstrated a significant increase of syncope in patients treated with AChEIs compared to placebo (odds ratio (OR): 1,9; 95%-CI 1,09-3,33). A similar increased risk of syncope was also observed in a different meta-analysis (OR: 1.53, 95%-CI 1.02-2.30 [16], without any increase in risk of falls and fractures. Though it cannot be concluded that the increased risk definitely resulted from AChEI therapy, cardio-inhibitory side effects of AChEI therapy were potentially involved, which is further supported with observational cohort data.

Observational data

Several case reports describe a potential association between therapy with AChEIs and occurrence of bradycardia, atrioventricular block, prolonged QTc interval or torsades de pointes [17-22]. A population-based study conducted by Park-Wyllie et al. investigated the relation between therapy with AChEIs and hospital admission for bradycardia [23]. The investigators compared 161 patients with bradycardia compared to 466 controls without bradycardia and concluded that therapy with AChEIs doubled the risk of admission for bradycardia (adjusted OR: 2,13; 95%-CI 1,29-3,51; p=0,003). Two large observational studies investigated the incidence of bradycardia, falls, syncope and pacemaker implantation in patients treated with AChEIs versus a non-treated control group. A first retrospective study in 19.803 patients treated with a AChEI showed a significantly increased incidence of bradycardia (Hazard ratio (HR) 1,69; 95%-CI 1,32-2,15), syncope (HR 1,76; 95%-CI 1,57-1,98), pacemaker implantation (HR 1,49; 95%-CI 1,12-2,00) and hip fracture (HR 1,18; 95%-CI 1,04-1,34) [24]. A second large study with 11328 AD patients treated with AChEIs demonstrated an increased incidence of bradycardia (HR 1,4; 95%-CI 1,1-1,7), falls (HR 2,6; 95%-CI 1,9-3,5), syncope (HR 3,7; 95%-CI 2,5-5,5) and pacemaker implantation (0,73% versus 0,17%) [25]. Incidence of fractures was comparable. These higher incidences of bradycardia were reported for all three AChEIs [9, 24, 25] though in the study of Hernandez daily administration of 5mg donepezil did not increase the risk of bradycardia (HR 1.1; 95% CI 0,85–1,5) compared to placebo, whereas higher doses did carry a significant risk [25]. Groups treated with galantamine or rivastigmine were too small to study any dose dependent effects. Also, these higher incidences were not associated with an increase in mortality. On the contrary, number of deaths was lower in the bradycardia group (HR 0,64; 95%-CI 0,52-0,79).

In a recent cohort crossover study 3358 Dutch AD patients were followed for 8,9 years [26]. The analysis was limited to galantamine and rivastigmine as donepezil is not authorized in the

Netherlands. There were 132 primary hospitalizations for atrioventricular block and 17 for syncope. Poisson regression showed increased incidence densities under AChEI therapy when compared to the period before AChEI initiation while Cox regression showed numerically increased HRs, none of which were statistically significant. Although AChEI exposure might increase the risk of some adverse cardiac events, the authors concluded that the small number of cases limited their analysis and that larger study samples would be needed.

In 2013, Nordstrom et al. published a large retrospective study of 7073 patients with AD or mixed dementia, in which AChEI use was associated with a 34% lower risk for myocardial infarction (MI) or death (HR 0,66; 95% CI 0,56–0,78) [27]. This reduction persisted when death and MI were analyzed separately. The associations were stronger with increasing doses. In the accompanying editorial it was again emphasized that more research was needed [28]. In an earlier smaller retrospective study, Sato et al. observed a similar association between decreased cardiovascular mortality and donepezil use in 156 patients suffering from AD and vascular dementia [29]. Donepezil use was associated with a lower risk for cardiovascular (HR 0,54; 95% CI 0.30-0,98) and total (HR 0,68; 95% CI 0,46-0,99) mortality.

In a subsequent small prospective study, donepezil did not reduce brain-natriuretic peptide (BNP) levels in elderly AD patients without symptomatic heart failure while significantly increasing the QTc [30]. No torsades de pointes were seen. The investigators did observe a reduction in BNP levels in patients with a baseline BNP value of >60pg/ml [30].

Cholinesterase inhibitors and the heart: friend or foe?

AChEIs indirectly influence peripheral as well as central receptors, as a result from the aspecific increase in the amount of ACh in the synaptic cleft. Cardiac ACh receptors are type M2 muscarinic receptors, present within the sinoatrial and atrioventricular node and myocardium [4]. Activation of these receptors by AChEI could theoretically result in negative chronotropic and dromotropic effects, clinically manifested as a decrease in heart rate, bradycardia or sino-atrial or atrioventricular block [17].

In vivo effects of therapy with AChEIs were investigated in animals, where treatment with the AChEI physostigmine resulted in a prolonged cardiac cycle length. In humans, pharmacological vagal stimulation would normally result in an increase of heart rate variability, a measure for cardiac parasympathic activity [31]. Also, local vagal neural stimulation by non-pharmacological means is currently being investigated in the treatment of chronic heart failure, a disease state that exhibits an increased sympathic and a disordered parasympathic innervation [32, 33]. AChEI administration however has resulted in reduced heart rate variability in some studies [34, 35], which could contribute to a higher incidence of cardiac adverse events.

Lowering the heart rate per se does not equal negative cardiovascular outcomes. Reduction of heart rate is related to better outcomes in patients with systolic heart failure in sinus rhythm as has been shown for ivabradine [36]. Ivabradine decreases heart rate by a selective dose-dependent inhibition of the funny current I_f, which effectively slows down the pacing at the sino-atrial node. At therapeutic concentrations ivabradine does not directly affect other aspects of cardiac function[37]. Digoxin, another heart-rate lowering drug has both bradycardic and positive inotropic properties. By increasing vagal tone it decreases sinus rate and slows AV conduction [38]. It has also been associated with an increase in heart rate variability, as opposed to donepezil. As mentioned above, AChEI will only decrease the heart rate by a few beats per minute, while ivabradine and digoxin will facilitate a larger reduction [39].

In vivo experiments showed prolonged QTc intervals after supratherapeutic doses of galantamine [40], and AChEIs were in some cases believed to be associated to a prolonged QTc interval [18, 19, 21, 22].

In vitro and animal studies have also shown limited cardioprotective effects of AChEI, especially donepezil. In high dose, it improved 50 day survival in a murine heart failure model and appeared to

have certain anti-inflammatory properties [41, 42]. In macrophages, the production of a pro-inflammatory cytokine was reduced, and in mice suffering MI and treated with donepezil, incidence of cardiac rupture during the acute phase of MI significantly decreased. Donepezil was also revealed to have anti-oxidant and anti-atherosclerotic properties in male apolipoprotein E knockout mice [43]. In summary, although adverse drug reactions can occur and are pharmacologically plausible, current evidence asks for a more nuanced view on prescribing AChEI in elderly patients. Nonspecific stimulation of cholinergic innervation could have some cardiovascular benefits, although this has not been investigated in adequately designed trials. In no way, we advocate the use of these drugs in the treatment of cardiovascular disease.

Factors putting patients at risk for cardiac effects?

While generally all AChEIs have a favorable cardiac safety profile and incidence of adverse events is low, it could be hypothesized that particular patient populations with pre-existing heart disease or taking cardio-inhibitory drugs could be at higher risk for cardiac adverse events when taking AChEIs. Data in this regard are however inconclusive. In the study demonstrating an increased incidence of hospital admissions for bradycardia in AChEI users [23], pre-existing cardiac comorbidity did not increase the risk (adjusted OR: 2,25; 95%-CI 1,18-4,28; p= 0,014) nor did the use of negative chronotropic drugs (adjusted OR: 2,34; 95%-CI 1,16-4,71 p=0,017). On the contrary, in the study of Hernandez [25], an elevated risk of a significant decrease in heart rate was observed in patients treated with beta-blockers, as well as in patients with a history of MI, hypertension or heart failure[25].

Concerning any influence on QTc, published data are reassuring [12, 13, 15, 44], although a few case reports have been published describing prolonged QTc in patients treated with donepezil, galantamine and rivastigmine. No data exist whether pharmacodynamic interactions with other QTc-prolongating drugs might increase the risk for cardiac adverse events. Also, it is hard to establish if an increased risk of syncope might be a consequence of an undiagnosed arrhythmia such as torsades de pointes. In 2005, Bordier et al. identified a probable cardiovascular cause of syncope (e.g. complete AV block) in over two-thirds of patients with AD who were treated with donepezil and were hospitalised for evaluation of syncope (n =16) [45].

Therefore, we plea for specific alertness when prescribing AChEIs in combination with drugs known to induce QTc prolongation Specific attention in this regards concerns the prescription of neuroleptics, often used in the treatment of behavioral disorders in patients simultaneously treated with AChEIs and known to prolong QTc-interval [46]. In any case, alternative non-pharmacological strategies should be regarded as a first line therapy for behavioral symptoms in AD.

Recommendations for practice

Adverse cardiac effects occur infrequently, but their consequences are potentially serious. Therefore, possible advantages of starting or continuing therapy with AChEIs should be weighed against potential risks. This estimation is not always straightforward, since effect sizes of clinical benefits of AChEI therapy vary and adverse effects are difficult to predict. Special consideration should go to patients at increased risk. Though no generally accepted guidelines for monitoring exist, some authors recommend to systematically obtain an ECG before therapy with AChEIs is started, in order to have baseline information available and for comparison purposes [47]; the evidence for this is however limited. Nevertheless, we do recommend special attention for cardiac side effects in all patients treated with AChEIs, which can be offered as suggested by a an adapted clinical protocol proposed by Rowland et al. [48] (Figure 1). With each patient contact (including before therapy start), a history-taking focusing on symptoms of cardiac side effects such as dizziness, falls, syncope is required, followed by registration of the heart frequency. After start of therapy, monthly follow-up is preferred during the titration phase until a stable dose has been reached followed by a 6-month interval control. If the patients' history is suggestive for cardiac side effects, and/or if heart rate

frequency is <50 bpm, further cardiac evaluation is recommended. With a heart rate between 50 and 60 bpm, alertfullness is required independent of the occurrence of any symptoms. While for galantamine and rivastigmine it is suspected but unknown whether a dose reduction would decrease the risk of cardiac adverse events, a lower dose (5mg) of donepezil decreased the risk of side effects to that of a control population [25].

In the presence of a history of bradycardia, arrhythmia or known QTc prolongation, or when taking drugs with negative chronotropic effects or with high risk of prolonging the QTc interval, we recommend a renewed history-taking at each visit and ECG monitoring before and during therapy, though no consensus guideline exist. In our experience and as suggested by Rowland et al. [48], a first-degree heart block is no contraindication for therapy with AChEIs but a more intensive clinical and ECG monitoring is advised. In case of a second-degree heart block, and certainly for a Mobitz type II, starting or continuing therapy should only be done after specialist advise.

Lastly, certain drugs might influence the pharmacokinetics of donepezil and galantamine by interacting with the hepatic CYP450 system (Table 1). Inhibition of CYP2D6 and/or CYP3A4 could at least theoretically result in a higher exposure for both drugs, potentially leading to adverse drug events while induction of these hepatic isoenzymes would result in a lower efficacy. Relevant data however are scarce. AChEIs should not be perceived as drugs with a narrow therapeutic index, unlike digoxin or warfarin. Nevertheless, although the clinical relevance of these interactions still needs to be determined, they are as a rule avoidable and in that sense interactions should be taken into account when monitoring AChEI therapy [49].

Conclusion

AChEIs are widely used and prescribed in the treatment of AD, and are generally safe to use also in an elderly population. Both beneficial and adverse cardiac effects have been related to AChEIs therapy, but serious adverse events related to this therapy are infrequent. Nevertheless, prescribers should be aware of the possible consequences of their prescriptions, and in the case of AChEIs negative chronotropic and dromotropic effects could occur. While several RCTs did not find any significant cardiac adverse effect, population based open label studies reported the infrequent occurrence of bradycardia, syncope, falls and pacemaker implantation, but use of AChEIs was also associated with a decreased risk ofMI or mortality. Because of its G1 selectivity, rivastigmine has a higher affinity for cerebral receptors; clinical evidence of a decreased cardiac risk compared to donepezil and galantamine is however not available. Patients diagnosed with cardiac disease or taking drugs with negative chronotropic of dromotropic effects are potentially at higher risk, though available data do not support this uniformly.

Prescribers of therapy with AChEIs should pay attention to clinical symptoms of cardiac adverse effects, and monitor the heart rate of their patients. In selected cases, it could be reasonable to perform ECG monitoring though no consensus exists. In some cases the advantages of starting or continuing therapy should be outweighed against potential disadvantages.

References

1. Bartus, R.T., et al., *The cholinergic hypothesis: a historical overview, current perspective, and future directions.* Ann N Y Acad Sci, 1985. **444**: p. 332-58.
2. Bartus, R.T., et al., *The cholinergic hypothesis of geriatric memory dysfunction.* Science, 1982. **217**(4558): p. 408-14.
3. Pepeu, G. and M.G. Giovannini, *Cholinesterase inhibitors and beyond.* Curr Alzheimer Res, 2009. **6**(2): p. 86-96.
4. Ebert, T., *Autonomic nervous system*, in *Foundations of anesthesia: basic and clinical sciences.*, H.H. Jr and H. PM, Editors. 2000, Mosbt: Londeon.
5. Millar, N.S. and C. Gotti, *Diversity of vertebrate nicotinic acetylcholine receptors.* Neuropharmacology, 2009. **56**(1): p. 237-46.
6. Mesulam, M., et al., *Widely spread butyrylcholinesterase can hydrolyze acetylcholine in the normal and Alzheimer brain.* Neurobiol Dis, 2002. **9**(1): p. 88-93.
7. Wilkinson, D.G., et al., *Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between*

pharmacological effects and clinical efficacy. Drugs Aging, 2004. **21**(7): p. 453-78.
8. Inglis, F., *The tolerability and safety of cholinesterase inhibitors in the treatment of dementia.* Int J Clin Pract Suppl, 2002(127): p. 45-63.
9. Birks, J., *Cholinesterase inhibitors for Alzheimer's disease.* Cochrane Database Syst Rev, 2006(1): p. CD005593.
10. Jann, M.W., K.L. Shirley, and G.W. Small, *Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors.* Clin Pharmacokinet, 2002. **41**(10): p. 719-39.
11. Rogers, S.L., et al., *Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group.* Arch Intern Med, 1998. **158**(9): p. 1021-31.
12. Feldman, H., et al., *A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease.* Neurology, 2001. **57**(4): p. 613-20.
13. Tariot, P.N., et al., *A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group.* Neurology, 2000. **54**(12): p. 2269-76.
14. Kumar, V., et al., *An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors.* Eur J Neurol, 2000. **7**(2): p. 159-69.
15. Morganroth, J., et al., *Electrocardiographic effects of rivastigmine.* J Clin Pharmacol, 2002. **42**(5): p. 558-68.
16. Kim, D.H., et al., *Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials.* J Am Geriatr Soc, 2011. **59**(6): p. 1019-31.
17. Bordier, P., et al., *Cardiovascular effects and risk of syncope related to donepezil in patients with Alzheimer's disease.* CNS Drugs, 2006. **20**(5): p. 411-7.
18. Fisher, A.A. and M.W. Davis, *Prolonged QT interval, syncope, and delirium with galantamine.* Ann Pharmacother, 2008. **42**(2): p. 278-83.
19. Tanaka, A., S. Koga, and Y. Hiramatsu, *Donepezil-induced adverse side effects of cardiac rhythm: 2 cases report of atrioventricular block and Torsade de Pointes.* Intern Med, 2009. **48**(14): p. 1219-23.
20. Leentjens, A.F. and J.A. Kragten, *[Complete atrioventricular block during galantamine therapy].* Ned Tijdschr Geneeskd, 2006. **150**(10): p. 563-6.
21. Nelson, M.W. and R.W. Buchanan, *Galantamine-induced QTc prolongation.* J Clin Psychiatry, 2006. **67**(1): p. 166-7.
22. Walsh, E. and J. Dourish, *Prolonged QT interval with rivastigmine.* Br J Psychiatry, 2002. **180**: p. 466.
23. Park-Wyllie, L.Y., et al., *Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study.* PLoS Med, 2009. **6**(9): p. e1000157.
24. Gill, S.S., et al., *Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study.* Arch Intern Med, 2009. **169**(9): p. 867-73.
25. Hernandez, R.K., et al., *Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the veterans affairs new England healthcare system.* J Am Geriatr Soc, 2009. **57**(11): p. 1997-2003.
26. Kroger, E., et al., *Use of rivastigmine or galantamine and risk of adverse cardiac events: a database study from the Netherlands.* Am J Geriatr Pharmacother, 2012. **10**(6): p. 373-80.
27. Nordstrom, P., et al., *The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease.* Eur Heart J, 2013. **34**(33): p. 2585-91.
28. Jeger, R.V., *Mens sana in corpore sano revisited*, in *Eur Heart J*. 2013: England. p. 2580-1.
29. Sato, K., et al., *The Effect of Donepezil Treatment on Cardiovascular Mortality.* Clin Pharmacol Ther, 2010. **88**(3): p. 335-8.
30. Kubo, T., et al., *Influences of donepezil on cardiovascular system--possible therapeutic benefits for heart failure--donepezil cardiac test registry (DOCTER) study.* J Cardiovasc Pharmacol, 2012. **60**(3): p. 310-4.
31. Masuda, Y., *Cardiac effect of cholinesterase inhibitors used in Alzheimer's disease--from basic research to bedside.* Curr Alzheimer Res, 2004. **1**(4): p. 315-21.
32. Singh, J.P., J. Kandala, and A. John Camm, *Non-pharmacological modulation of the autonomic tone to treat heart failure.* Eur Heart J, 2013.
33. Hamann, J.J., et al., *Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure.* Eur J Heart Fail, 2013. **15**(12): p. 1319-26.
34. Umegaki, H. and O. Khookhor, *The response of the autonomic nervous system to the cholinesterase inhibitor, donepezil.* Neuro Endocrinol Lett, 2013. **34**(5): p. 383-7.

35. McLaren, A.T., et al., *Cardiovascular effects of donepezil in patients with dementia.* Dement Geriatr Cogn Disord, 2003. **15**(4): p. 183-8.
36. Bohm, M., et al., *Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial.* Lancet, 2010. **376**(9744): p. 886-94.
37. Borer, J.S. and J.Y. Le Heuzey, *Characterization of the heart rate-lowering action of ivabradine, a selective I(f) current inhibitor.* Am J Ther, 2008. **15**(5): p. 461-73.
38. Dobre, D., et al., *Heart rate: a prognostic factor and therapeutic target in chronic heart failure. The distinct roles of drugs with heart rate-lowering properties.* Eur J Heart Fail, 2013.
39. Castagno, D., et al., *Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure.* Eur Heart J, 2012. **33**(9): p. 1137-41.
40. Vigneault, P., et al., *Galantamine (Reminyl) delays cardiac ventricular repolarization and prolongs the QT interval by blocking the HERG current.* Eur J Pharmacol. **681**(1-3): p. 68-74.
41. Handa, T., et al., *Anti-Alzheimer's drug, donepezil, markedly improves long-term survival after chronic heart failure in mice.* J Card Fail, 2009. **15**(9): p. 805-11.
42. Arikawa, M., et al., *Donepezil, anti-Alzheimer's disease drug, prevents cardiac rupture during acute phase of myocardial infarction in mice.* PLoS One, 2011. **6**(7): p. e20629.
43. Inanaga, K., et al., *Acetylcholinesterase inhibitors attenuate atherogenesis in apolipoprotein E-knockout mice.* Atherosclerosis, 2010. **213**(1): p. 52-8.
44. Isik, A.T., et al., *Which cholinesterase inhibitor is the safest for the heart in elderly patients with Alzheimer's disease?* Am J Alzheimers Dis Other Demen, 2012. **27**(3): p. 171-4.
45. Bordier, P., et al., *Causes of syncope in patients with Alzheimer's disease treated with donepezil.* Drugs Aging, 2005. **22**(8): p. 687-94.
46. Mackin, P., *Cardiac side effects of psychiatric drugs.* Hum Psychopharmacol, 2008. **23 Suppl 1**: p. 3-14.
47. Malone, D.M. and J. Lindesay, *Cholinesterase inhibitors and cardiovascular disease: a survey of old age psychiatrists' practice.* Age Ageing, 2007. **36**(3): p. 331-3.
48. Rowland, J.P., et al., *Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol.* Advances in Psychiatric Treatment, 2007. **13**: p. 178-184.
49. Noetzli, M. and C.B. Eap, *Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease.* Clin Pharmacokinet, 2013. **52**(4): p. 225-41.

Table 1. Commonly used inhibitors of cytochrome P450 enzymes (CYP2D6 and CYP3A4) in older persons.

CYP3A4 Inhibitors	CYP2D6 Inhibitors
Diltiazem	Fluoxetine
Verapamil	Haloperidol
Itraconazole	Paroxetine
	Amiodarone
Ketoconazole	
Clarithromycin	
Erythromycin	
Grapefruit juice	
Amiodarone	
Amlodipine	

Figure 1. Clinical protocol for initiation or continuation of AChEI therapy in asymptomatic and symptomatic patients (adapted from [48]).